

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



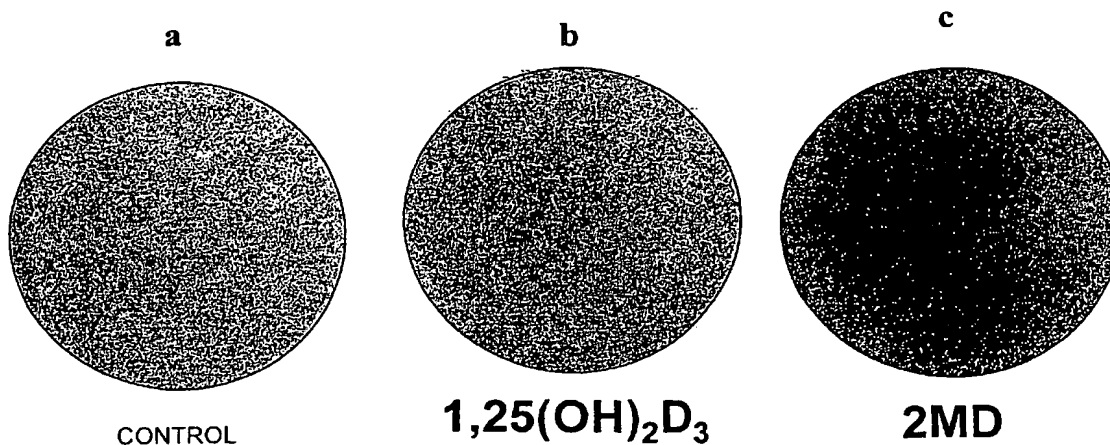
(43) International Publication Date
9 October 2003 (09.10.2003)

PCT

(10) International Publication Number
WO 03/082300 A1

- (51) International Patent Classification⁷: **A61K 31/59**, 31/593, A61P 3/14, 3/02
- (21) International Application Number: PCT/US03/07443
- (22) International Filing Date: 12 March 2003 (12.03.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
10/105,826 25 March 2002 (25.03.2002) US
- (71) Applicant: **WISCONSIN ALUMNI RESEARCH FOUNDATION** [US/US]; 614 Walnut Street, Madison, WI 53705 (US).
- (72) Inventors: **DELUCA, Hector, F.**; 1809 Highway BB, Deerfield, WI 53531 (US). **PIKE, J., Wesley**; 9109 Settler's Road, Madison, WI 53717 (US). **SHEVDE, Nirupama, K.**; 9109 Settler's Road, Madison, WI 53717 (US).
- (74) Agents: **WOZNY, Thomas, M.** et al.; Andrus, Scales, Starke & Sawall, LLP, 100 East Wisconsin Avenue, Suite 1100, Milwaukee, WI 53202 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF CARBON-2-MODIFIED-VITAMIN D ANALOGS TO INDUCE THE FORMATION OF NEW BONE



(57) **Abstract:** It has been discovered that the 2-carbon-modified derivatives of 1 α ,25-dihydroxyvitamin D₃ specifically stimulate osteoblasts to form new bone. The ability of the 2-carbon-modified vitamin D analogs to stimulate new bone formation suggest that these compounds can be used where synthesis of new bone is required. Thus, these compounds can be used either systemically or locally to stimulate the growth of bone transplants, to increase the rate of fracture healing and thereby reduce the time required for the healing of fractures, the stimulation of bone growth when required for replacement surgery, and also for the growth of bone to implants or other devices required to maintain the skeleton or teeth in the proper positions.

BEST AVAILABLE COPY

WO 03/082300 A1

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/07443

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/59 A61K31/593 A61P3/14 A61P3/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, EMBASE, BIOSIS, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 74766 A (WISCONSIN ALUMNI RES FOUND) 11 October 2001 (2001-10-11) page 6 -page 7; claim 31	1-10, 20, 23-28 1-20
Y	---	
X	WO 98 41501 A (WISCONSIN ALUMNI RES FOUND) 24 September 1998 (1998-09-24) abstract; claims 1, 11-16, 29, 36-45 page 29-30 page 7, line 23, 24 page 11, line 1-4	1-10, 20, 23-28 1-20
Y	---	
X	WO 02 05823 A (WISCONSIN ALUMNI RES FOUND) 24 January 2002 (2002-01-24) abstract page 3 -page 5, line 7 page 10 -page 11	1-10, 20, 23-28

	-/-	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

11 July 2003

Date of mailing of the international search report

29/07/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Ansaldo, M

INTERNATIONAL SEARCH REPORT

Intel onal Application No
PCT/US 03/07443

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 41500 A (WISCONSIN ALUMNI RES FOUND) 24 September 1998 (1998-09-24) page 6, line 26; claims 1,11-21,28-35 -----	1-9,21, 23-28
X	WO 02 05824 A (WISCONSIN ALUMNI RES FOUND) 24 January 2002 (2002-01-24) page 3, line 5 -page 5 page 8-10 -----	1-9,21, 23-28
X	SICINSKI ET AL: "New 1alpha-25-Dihydroxy-19-norvitamin D3 Compounds of High Biological Activity: Synthesis and Biological Evaluation of 2-Hydroxymethyl, 2-Methyl, and 2-Methylene Analogues" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 41, 22 October 1998 (1998-10-22), pages 4662-4674, XP002106465 ISSN: 0022-2623 abstract -----	1,10,20, 21,23-28
Y	WO 97 11053 A (WISCONSIN ALUMNI RES FOUND ;DELUCA HECTOR F (US); SCHNOES HEINRICH) 27 March 1997 (1997-03-27) page 5 -page 8 -----	1-9, 11-19
P,X	SHEVDE NIRUPAMA K ET AL: "A potent analog of 1alpha,25-dihydroxyvitamin D3 selectively induces bone formation." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. UNITED STATES 15 OCT 2002, vol. 99, no. 21, 15 October 2002 (2002-10-15), pages 13487-13491, XP002247340 ISSN: 0027-8424 abstract -----	1-10,20, 23-28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/07443

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-28 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/07443

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0174766	A	11-10-2001	US 6392071 B1 AU 4790501 A CA 2404548 A1 EP 1268416 A1 US 2002087015 A1 WO 0174766 A1	21-05-2002 15-10-2001 11-10-2001 02-01-2003 04-07-2002 11-10-2001
WO 9841501	A	24-09-1998	US 5843928 A AT 223890 T AU 714253 B2 AU 6280198 A DE 69807852 D1 DK 970047 T3 EP 0970047 A1 ES 2179451 T3 JP 2001504135 T NO 994398 A NZ 337503 A PT 970047 T US 2002087015 A1 WO 9841501 A1 US 5936133 A US 6392071 B1	01-12-1998 15-09-2002 23-12-1999 12-10-1998 17-10-2002 11-11-2002 12-01-2000 16-01-2003 27-03-2001 10-09-1999 29-09-2000 31-01-2003 04-07-2002 24-09-1998 10-08-1999 21-05-2002
WO 0205823	A	24-01-2002	AU 7888801 A CA 2416194 A1 EP 1301189 A2 WO 0205823 A2	30-01-2002 24-01-2002 16-04-2003 24-01-2002
WO 9841500	A	24-09-1998	US 5945410 A AU 714390 B2 AU 6280098 A BR 9808010 A EP 0971888 A1 JP 2000513010 T NO 994489 A NZ 337262 A US 2002151528 A1 WO 9841500 A1 US 6127559 A US 2003073857 A1 US 6277837 B1 US 6316642 B1 US 6306844 B1 US 2002123638 A1	31-08-1999 23-12-1999 12-10-1998 08-03-2000 19-01-2000 03-10-2000 16-09-1999 29-09-2000 17-10-2002 24-09-1998 03-10-2000 17-04-2003 21-08-2001 13-11-2001 23-10-2001 05-09-2002
WO 0205824	A	24-01-2002	US 6306844 B1 AU 7330301 A CA 2416187 A1 EP 1305030 A1 WO 0205824 A1 US 2002151528 A1	23-10-2001 30-01-2002 24-01-2002 02-05-2003 24-01-2002 17-10-2002
WO 9711053	A	27-03-1997	US 5952317 A AU 717238 B2 AU 7242696 A CA 2229316 A1 EP 1021401 A1	14-09-1999 23-03-2000 09-04-1997 27-03-1997 26-07-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/07443

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9711053	A	HU 9802303 A2	01-02-1999
		JP 11511475 T	05-10-1999
		JP 3372259 B2	27-01-2003
		NO 981282 A	22-05-1998
		NZ 319819 A	28-02-2000
		NZ 501318 A	27-07-2001
		WO 9711053 A1	27-03-1997